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REDUCED INCIDENCE OF PERSISTENT CHROMOSOME ABERRATIONS IN MICE IRRADIATED AT LOW DOSE-RATE

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ABSTRACT

A marked difference in the production of persistent chromosome aberrations in mouse marrow cells by ionizing radiation delivered at a high dose rate (30 rad/min) versus a low dose rate (1.45 rad/hour) was observed. Clones of cell with chromosome abnormalities were present in the marrow of <u>all</u> the mice previously exposed to the X rays, either a single dose or fractionated, at 30 rad/min. The frequency of chromosome aberrations in these mice varied from 14% to 72% of the cells examined. By contrast, <u>none</u> of the 17 mice exposed to the continuous low dose rate gamma radiation (1.45 rad/hour) showed definite clones of abnormal marrow cells, and the frequency of persistent chromosome aberrations varied from zero to 8% in this group. The possible basis for this marked reduction in the production of persistent chromosome changes in marrow cells following exposure to low dose-rate gamma radiation is briefly discussed. If some of the late effects of radiation, particularly leukemia incidence, are related to the frequency of chromosome aberrations, it is possible that low dose-rate gamma radiation may be less leukemogenic than high dose-rate radiation.

SUMMARY

The Problem:

An important aspect of the problem of radiation hazard evaluation relates to the effect of radiation dose-rate. Although it is known that dose-rate influences the degree of acute biological damage, as evidenced for example by the change in LD_{50}, relatively little information is available on the influence of radiation dose-rate on the late consequences of radiation damage, particularly at the cellular level. The availability of a low dose-rate Co^{60} facility provided the opportunity for comparison of the effects of low dose-rate gamma radiation and high dose-rate X radiation on the occurrence of chromosomal aberrations in bone marrow cells in mice.

The Findings:

Young adult LAF_1 mice were exposed to one of the following radiation schedules: a single dose of 500 rad of X rays delivered at a dose-rate of 30 rad per minute; fractionated X rays: 100 rad given daily (dose-rate 30 rad/min) for 9 exposures for a total of 900 rad; Co^{60} gamma radiation given continuously at a dose-rate of 1.45 rad/ hour for a total dose of 926 rad or 935 rad. Chromosome preparations

were made from the bone marrow at 1 to 19 months after irradiation. The experimental data show that clones of cells with chromosome abnormalities were present in the marrow of all the mice previously exposed to the X rays, either a single dose or fractionated, at 30 rad/min. The frequency of chromosome aberrations in these mice varied from 14% to 72% of the cells examined. By contrast, none of the 17 mice exposed to the continuous low dose rate gamma radiation (1.45 rad/hour) showed definite clones of abnormal marrow cells, and the frequency of persistent chromosome aberrations varied from zero to 8% in this group. The possible basis for this marked reduction in the production of persistent chromosome changes in marrow cells following exposure to low dose-rate gamma radiation is briefly discussed. If some of the late effects of radiation, particularly leukemia incidence, are related to the frequency of chromosome aberrations, it is possible that low dose-rate gamma radiation may be less leukemogenic than high dose-rate radiation.

INTRODUCTION

The importance of radiation dose-rate in the delayed and late effects of ionizing radiation has been demonstrated, both with respect to genetic effects (mutations) in mice (1,2), and in life span studies (3). However, since no observations on persistent radiation-induced chromosome abnormalities relative to dose-rate are available, we have been interested in obtaining such data, and in correlating them with late pathological changes after irradiation at high and low dose-rates.

MATERIALS AND METHODS

Chromosome studies were done on the bone m [illegible] of female LAF_1 mice irradiated at 2 - 3 months of age as follows:

Group 1 - A single dose of 500 rad of X rays, delivered at a dose-rate of 30 rad per minute as measured in air.

Group 2 - Fractionated X rays; 100 rad given on 9 of 11 successive days, for a total dose of 900 rads; dose-rate 30 rad per minute.

Group 3 - Co^{60}-gamma radiation, given continuously at a dose-rate of 1.45 rad per hour, for a total dose of 926 or 935 rad.

The radiation factors for the X radiation were: 250 kv , 15 ma, HVL 1.5 mm Cu, filter 0.5 mm Cu plus 1 mm Al, TSD 100 cm. For the Co^{60} irradiation, mice were placed in Lucite cages, which were positioned around a 10 curie source which has been described previously (4). The dose-rate was measured at the midpoint of the cage, using 5 minute readings with a 250 mr chamber. The mean value for dose-rate was 1.45 rad/hour as of August 4, 1961. Appropriate corrections were made for decay of the source at the time of exposure. Since the duration of exposure was approximately one month, it was necessary to remove the mice from the source periodically for brief periods, in order to feed and water them, and to clean the cages. The total "off-time" during the entire exposure was 7 hours.

At various times from 1 to 19 months after irradiation, air-dried chromosome preparations were made from the bone marrow of each mouse according to techniques previously described (5). Fifty good metaphases from each animal were examined.

RESULTS

Chromosome changes observed in the irradiated mice are given in Table I. Because of the uniform morphology of mouse chromosomes, all having terminal centromeres, the only aberrations recognizable are those producing aneuploidy or else a marker chromosome obviously longer or shorter than the normal complement, or with a centromere which is not terminal (6). Inspection of the table indicates that the most

TABLE 1

Chromosome Chang s in Marrow Cells of Mice Irradiated at Different Dose Rates

ANIMAL NO.	TOTAL DOSE	DOSE RATE	INTERVAL AFTER IRRADIATION	CHROMOSOME ABERRATIONS (NO./50 CELLS) MINUTE + ABNORMALLY LONG	MINUTE	ABNORMALLY LONG	OTHER	TOTAL ABERRATIONS (%)	CLONAL ABERRATIONS (%)
1	500 rad	30 rad/m 1	3 mo.	22			1	46	44
2	"	"	3 "	9				18	18
3	"	"	13 "	7	4	2		26	14
4	"	"	13 "		3	15		36	30
5	"	"	13 "	7				14	14
6	"	"	13 "	9	8			34	18, 16
7	"	"	13 "	5	3	1		18	10
8	"	"	18 "		5		18*	46	10, 36
9	"	"	18 "	10	1	2	23**	72	20, 46
10	900 rad (100 rad x 9)	"	19 "			21		42	42
11	"	"	19 "		6	1		14	12
12	"	"	19 "	5	6	2		26	10, 12
13	935 rad	1.45 rad/	1 wk					0	0
14	"	"	1 "		3			6	0
15	"	"	1 "			1		2	0
16	"	"	1 "		1			2	0
17	"	"	1 "			1		2	0
18	"	"	1 "		1			2	0
19	"	"	4 "					0	0
20	"	"	4 "	2	1			6	0
21	"	"	5 "	3		1		8	0
22	"	"	5 "			1		2	0
23	926 rad	"	12 mo.					0	0
24	"	"	"					0	0
25	"	"	"		1			2	0
26	"	"	"				1	2	0
27	"	"	"		1			2	0
28	"	"	"					0	0
29	"	"	"		1			2	0

* 41 chromosomes (one abnormally ong)

** 39 chromosomes (one metacentric

commonly observed change was an apparent reciprocal translocation resulting in two markers, an abnormally long chromosome and a "minute" (Figure 1). It was, of course, impossible to determine if morphologically similar changes in different animals, or even in different cells, involved identical chromosomes.

In those mice in which the marrow cells showed a high frequency of chromosome aberrations, these were generally of only 1 or 2 types in a given animal. Thus, the abnormal cells appeared to be largely in the form of "clones" or "stemlines" derived from only 1 or 2 radiation-damaged precursors (7). For the purpose of tabulation, any group of 5 or more cells having the same morphological chromosome change was considered to represent a clone (e.g., 10% or more of the cells examined).

The data indicate that clones of cells with chromosome abnormalities were present in the bone marrow of all 9 mice previously exposed to a single X-ray dose of 500 rad given at a dose rate of 30 rad/min. (Group 1), as well as in the three mice exposed to fractionated X radiation (100 rad x 9) given daily at a dose rate of 30 rad/min. (Group 2). The frequency of cells with aberrations varied from 14% to 72%, without any obvious effect of the length of time between irradiation and sacrifice (3 to 19 months). It may be significant that the two mice in Group 1 examined 18 months after exposure (the longest period in this group) showed the most profound chromosome changes. Abnormal cells constituted 46% and 72% respectively of their marrows, and these included the only two aneuploid clones observed, one with 41 chromosomes

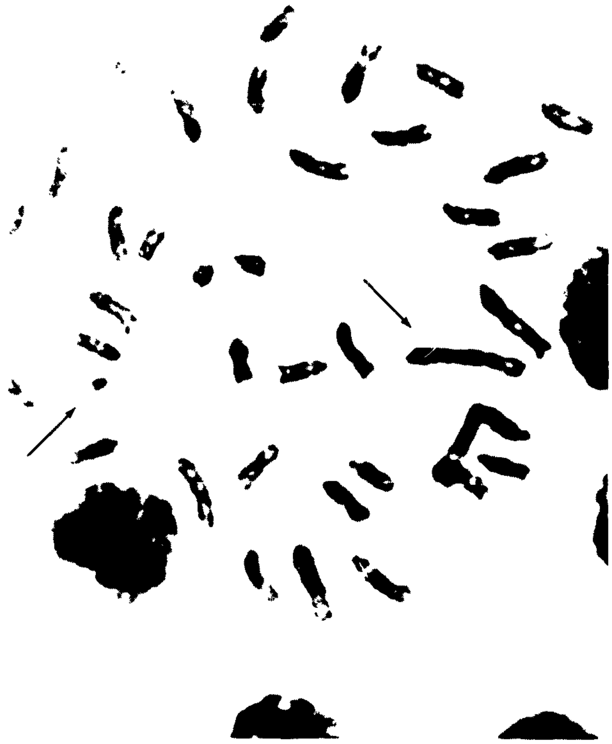

Fig. 1 Metaphase from bone marrow of LAF_1 mouse X-irradiated (500 rad) 18 months previously. Note an abnormally large and a minute chromosome (arrows). Twenty percent of the marrow cells examined were of this type.

and one with 39 chromosomes. The possibility of incipient leukemia in these two mice might be suggested by the chromosome findings (6,8), but neither these nor any other mice in the present study showed clinical or hematological evidence of the disease.

Definite clones of abnormal marrow cells were not observed in any of the 17 mice exposed to continuous low dose-rate Co^{60}. Gamma-radiation (1.45 rad/hr.) for a total dose of 926 or 935 rad (Group 3). Frequency of persistent chromosome aberrations varied from zero to 8% in this group, and in no animal did more than 65% of the cells show the same chromosome change. Some of these mice were examined within one week of the end of irradiation, and others up to a year later.

Unstable chromosome changes, such as acentric fragments, dicentrics, and rings were not observed in the present studies. Such aberrations were undoubtedly eliminated within one or two cell divisions after irradiation (6). The only unstable changes observed were occasional chromatid breaks, present in less than 2% of the cells from all groups.

DISCUSSION

The findings indicate a marked difference in the production of persistent chromosome changes in mouse marrow by ionizing radiation delivered at a high dose rate (30 rad/min.) versus a low dose rate (1.45 rad/hr). All of the animals exposed to the high dose rate showed clones of cells with chromosome abnormalities persisting in the marrow up to 19 months after irradiation. The mice exposed at the low dose

rate showed no definite clones and only a few random aberrations. These chromosome data correlate well with the observations of Russell,et al. (1,2) on the influence of radiation dose-rate on mutation frequency in mice: Following exposure to X radiation at low dose rates (90 r/week), the incidence of specific locus mutations was one-third to one-half that in mice exposed to X rays at high dose rates (80-90 r/minute). The present findings would appear to be, on the chromosome level, the counterpart of these observations. Russell, et al. have also provided evidence that the dose-rate effect on mutation frequency "is an intracellular one and not a consequence of cell selection" (2). The rarity of persistent chromosome abnormalities after low dose-rate radiation could be similarly due to an intracellular recovery process, perhaps involving restitution and repair of radiation-induced chromosome breaks comparable to that observed by Wolff (9) in plant cells. This recovery process would presumably be analogous to that described by Elkind and Sutton (10) in studies of the viability of hamster cells in tissue culture after fractionated radiation. In their work, however, irradiation was completed within one mitotic cycle cycle, while in our low dose-rate experiments, numerous cell generations were involved. Hence, it is possible that additional recovery mechanisms, both intracellular and extracellular, might operate in our system.

It is also possible that both the high and low dose rates may have produced the same amount of non-recoverable chromosome damage,

and that cell selection rather than intracellular recovery mechanisms are responsible for the observed difference in persistent chromosome changes. The extensive destruction of marrow cells which occurs at the high dose rate, briefly producing an aplastic marrow, could provide the opportunity and "space" for a few stem cells, with radiation-induced chromosome changes conferring a slight growth advantage, to repopulate the marrow with recognizable clones. Cells with similar changes produced by low dose-rate radiation, which does <u>not</u> deplete the marrow, might not have a sufficient selective advantage to permit them to overgrow an already populated marrow; and, hence, they would continue to survive as only a small proportion of the marrow cells. The continued persistence of large clones of abnormal cells in the high dose-rate animals without concomitant hematological disorders indicates that radiation-induced chromosome abnormalities do not necessarily confer either a marked selective advantage or disadvantage on cells bearing them (6).

The present study permits further speculation on the relationship of radiation-induced chromosome changes to leukemogenesis. Data from both mice and humans indicate that there is no uniform correlation between demonstrable chromosome changes produced by radiation at high dose rates and the subsequent development of leukemia (6). Whether the incidence of radiation-induced leukemia in mice exposed to chronic low dose-rate gamma-radiation would parallel the present chromosome findings remains to be determined. Single acute exposure at a high dose rate, how-

ever, may be lethal for a larger number of marrow stem cells than is low dose-rate radiation, thus possibly eliminating many potentially leukemic cells from the "pool"---the so-called "therapeutic" effect of high radiation dose on leukemia incidence (11). If leukemogenesis is related to the total number of point mutations produced, it is conceivable that the frequency of point mutations could be the same in all 3 groups in the present study and that the leukemia incidence might actually be highest in the group receiving the low dose-rate exposure, as a result of accumulation of such radiation-induced point mutations with a minimum of cell killing. Observations on leukemia incidence in mice exposed to low dose-rate gamma-radiation are now being made.

The relationship between chromosome aberrations and the occurrence of other late pathological effects of irradiation such as solid tissue tumors, nephrosclerosis, and other lesions resulting in shortened life span is even less clear. Chromosome data are not available on the organs involved, and extrapolation to these tissues from dose-rate effects on bone marrow cells might well be erroneous, because of the great differences in mitotic rates and cell turnover. It will be of interest to attempt to assess the importance of chromosome damage in the production of late radiation effects in organs such as the liver and kidney.

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